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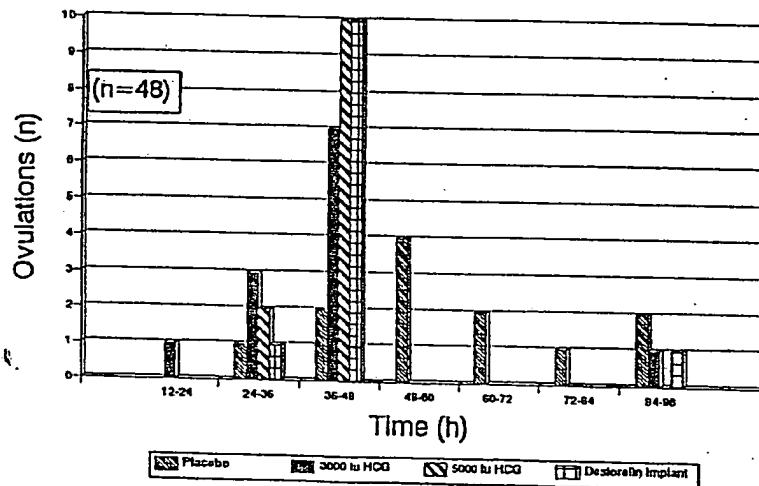
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(54) Title: BIOCOMPATIBLE IMPLANT FOR THE TIMING OF OVULATION IN MARES

Fig 1: Time to ovulation
Treatment: Follicle diameter 40mm



(57) Abstract

The induction of ovulation in mares having a maturing ovarian follicle is controlled by implanting into the mare a solid biocompatible implant comprising a solid carrier and an effective amount of leutinising hormone releasing hormone (LHRH) or an agonist of LHRH such as Deslorelin. The solid carrier is preferably a biologically absorbable inorganic salt mixed with an organic tablet release compound.

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BIOCOMPATIBLE IMPLANT FOR THE TIMING OF OVULATION IN MARES
FIELD OF THE INVENTION

The present invention relates to a method for controlling the timing of the ovulation of mares and to a
5 biocompatible implant for use in such a method.

BACKGROUND ART

The equine industry worldwide is continually improving breeding management. This improvement is driven by many factors; of significance are (i) the need to
10 conserve "stallion power" and (ii) the veterinarians requirement to improve their efficiency by having mares ovulate with more predictability.

In order to achieve the above, the ability to predict, within predetermined time constraints when a mare
15 will ovulate, is critical. The use of injection of human chorionic gonadotrophin (hCG) to stimulate ovulation in mares between 36-48 hours after application is widespread. However, despite success with this hormone, it has a number of serious drawbacks.

20 They include:

- (i) it is not registered for this use in many countries (USA, and areas of Europe). Veterinarians using hCG in countries where it is unregistered are liable for any claims against failure of the product.
- 25 (ii) continued used in the same mare can cause refractiveness - anaphylaxis is a possibility.
- (iii) hCG is derived from human urine either from pregnant or post menopausal women. Collection, isolation and purification are unpleasant, and the possibility of
30 transmission of disease, particularly those of viral origin, is a risk.
- (iv) supplies of hCG cannot be guaranteed.

As an alternative to hCG, Leutinising Hormone Releasing Hormone (LHRH) has been injected into mares to
35 stimulate ovulation. LHRH is also known as Gonadotrophin

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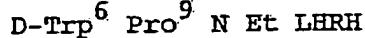
releasing hormone (GnRH). The LHRH stimulates the mare to produce its own gonadotrophin which, in turn, stimulates ovulation. An agonist of LHRH (Buserelin) has also been injected into mares and it has been reported that 5 ovulation may be induced by such injections. Injected hormones must be typically administered a number of times to be successful and they are required in relatively large doses.

10 DISCLOSURE OF THE INVENTION
The present invention is directed to an alternative method and composition for controlling the timing of ovulation in mares.

15 In a first aspect the present invention consists in a method for the controlled induction of ovulation in mares comprising implanting into a mare having a maturing ovarian follicle a solid biocompatible implant comprising a solid carrier and an effective amount of LHRH or an agonist of LHRH.

20 In a second aspect the present invention consists in a solid biocompatible implant for controlling the induction of ovulation in mares, the implant comprises a biologically absorbable solid and LHRH or an agonist of LHRH.

25 Deslorelin is a peptide and a super agonist for LHRH. It is the most preferred LHRH agonist for use in the present invention. The formula for Deslorelin is:-



(p Glu His Trp Ser Tyr D-Trp Leu Arg Pro NH₂)

30 Deslorelin has the particular advantage that its efficacy in the induction of ovulation in mares is sufficiently high that the biocompatible implant may be made small enough to be very acceptable in practice. There are however a number of other LHRH agonists which 35 could be used in carrying out the present invention.

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these include the following compounds as discussed in Dutton, A.S., "Luteinizing Hormone - Releasing Hormone (LHRH) Agonists", Drugs of the Future, Vol 13, No. 1, 1988:-

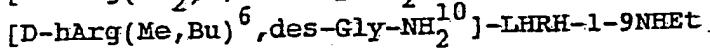
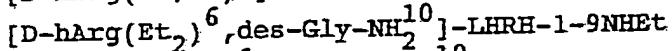
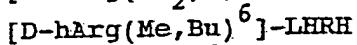
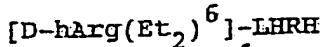
5

	Agonist Structure	Name (Company)
	[D-Ser(Bu) ⁶ .des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt	Buserelin (Hoechst)
	[D-Trp ⁶]·LHRH	Tryptorelin (Debiopharm) (Decapeptyn)
10	[des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt	Fertirelin (Takeda)
	[D-His(Bz) ⁶ , des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt	Histrelin (Ortho)
	[D-Leu ⁶ , des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt	Leuprolide (Abbott)
	[D-Trp ⁶ ,MeLeu ⁷ , des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt	Lutrelin (Wyeth)
	[D-Nal(2) ⁶]·LHRH	Nafarelin (Syntex)
15	[D-Ser(Bu) ⁶ , Azgly ¹⁰]·LHRH	Zoladex (Registered Trade Mark) ICI

In addition the following LHRH agonists may be used in carrying out the invention:-

	[D-Ser(Bu) ^t ⁶ ,]-LHRH(1-9)NHEt
20	[D-Lys(Boc) ⁶ ,des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt
	[D-Glu(OBu) ^t ⁶ ,des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt
	[D-Asp(OBu) ^t ⁶ ,des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt
	[D-Leu ⁶ Ser(Bu) ^t ⁷ ,des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt
	[D-Ser(Bu) ^t ⁶ ,Cys(Bu) ^t ⁷ des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt
25	[D-Ser(Bu) ^t ⁶ ,Ser(Bu) ^t ⁷ des-Gly-NH ₂ ¹⁰]·LHRH(1-9)NHEt
	[D-Phe ⁶ ,Azgly ¹⁰]·LHRH
	[D-Tyr(Me) ⁶ ,Azgly ¹⁰]·LHRH
	[D-Ser(Bu) ^t ⁶ ,Azgly ¹⁰]·LHRH
	[D-Tmo ⁶]·LHRH
30	[D-Nal(2) ⁶]·LHRH
	[D-Ptf ⁶]·LHRH
	[D-Tmp ⁶]·LHRH
	[D-Bpal ⁶]·LHRH
	[D-Nal(2) ⁶ MeLeu ⁷]·LHRH
35	[D-Nal(2) ⁶ MeLeu ⁷ ,des-Gly-NH ₂ ¹⁰]·LHRH-1-9NHEt

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- 5 The solid carrier for the LHRH or LHRH agonist should
be a material into which the Deslorelin can be mixed or
absorbed, onto which it may be adsorbed, or onto which it
may be coated. It is a particularly preferred feature of
the invention that the carrier is a biologically adsorbable
10 inorganic salt such as calcium phosphate dihydrate, calcium
phosphate, sodium sulphate or calcium carbonate. This
allows the biocompatible implant to be made cheaply by a
simple tabletting technique. To assist in forming the
implant and to provide an improved active release profile
15 it is preferred that the implant contains a small
proportion of an organic tablet release compound or
lubricating agent such as a fatty acid or a hydrogenated
vegetable oil. The tablet release compound preferably
comprises from 4 to 10% by weight of the implant and more
20 preferably about 8%. It has been found that the release
characteristics of the LHRH agonist from such an inorganic
salt mixed with such lubricating agent is such that
ovulation can be induced in a tightly controlled manner,
25 i.e., that a high proportion of the mares will ovulate at a
given time after the administration of the implant.

- The implant is desirably as small as possible.
Preferably the implant is substantially cylindrical having
a diameter of from 0.5 to 5mm and a length of from 1 to
30 6mm. Obviously other sizes and shapes of biocompatible
implants may be used however the selection of preferred
embodiments of the present invention allows the size of the
implant to be sufficiently small to be of practical
utility. The implant is preferably small enough to be able
35 to be implanted into a mare through a tubular needle. The

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needle is inserted into the mare, such as in the neck region, and the implant pushed down the needle with an obturator as the needle is withdrawn. This leaves the implant embedded subcutaneously in the animal. The LHRH agonist is released from the implant in a controlled manner and the carrier is slowly dissolved.

The LHRH agonist should preferably be present in the implant in an amount of from 1.0 to 5.0mg, more preferably 1.5 to 3.0mg and most preferably 2.0 to 2.4mg for a 10 thoroughbred mare of average size.

BRIEF DESCRIPTION OF THE DRAWINGS

Hereinafter given by way of example only are preferred embodiments of the present invention described with reference to the accompanying figures in which:-
15 Fig. 1 shows time to ovulation for mares treated as described in Example 1;

Fig. 2 shows time to ovulation after treatment with a short term implant containing 2.25mg of LHRH as described in Example 2; and
20 Figs. 3 to 6 show ovulation response to treatments as described in Example 3.

BEST METHOD FOR CARRYING OUT THE INVENTION

In all examples, unless indicated otherwise, short term implants of the LHRH agonist Deslorelin were prepared
25 by mixing the Deslorelin with finely ground calcium carbonate and 5% of a hydrogenated vegetable oil tableting aid sold under the trade mark "LUBRITAB" (Edward Mendell Co. Inc, New York, U.S.A). The mixture is then tableted to the desired shape in a conventional manner. The implants
30 were substantially cylindrical having a diameter of 2.3mm and a length of 3.4mm. All treatments with hCG were by injection.

Example 1

Groups of twelve Hannoverian mares were each given a
35 placebo implant, injected with either 3,000 iuhCG or with

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5,000 iuhCG or given an implant containing 1.5mg of Deslorelin. In this example treatment was given when the mares showed follicles of 40mm diameter as the horses were Hannoverian. The results of this example are shown in Fig.

- 5 1. It can be seen that the 1.5mg Deslorelin implant performed as well as 3,000 iuhCG and possibly as well as 5,000 iuhCG.

Example 2

10 The procedure of Example 1 was repeated with twenty seven Hannoverian mares being given a short term implant containing 2.25mg of Deslorelin. It can be assumed that those mares ovulating at 0-24 hours would have ovulated in the absence of treatment. The results obtained in this example are shown in Fig. 2.

15 Example 3

Groups of mares were each given a placebo implant, a 1.3, 1.6 or 2.2mg Deslorelin implant, or 5,000 iuhCG. The placebo treatment is designated 101 in Fig. 6 and the Deslorelin implants are indicated, respectively, as 102, 20 104 and 100.

It can be seen that the variation in ovulation was less for the 2.2mg treatment than all other treatments; ovulation commonly occurred around 48 hours post-implantation with this treatment.

25 Some data has been removed from the analyses as outliers in this trial. The criteria for removal was: those animals ovulating within 24 hours or 8+ days after implantation were considered not to have been affected by the implant. The numbers removed were 2 x hCG; 5 x 100, 2 30 x 101, 0 x 102 and 2 x 104.

Example 4

Mares with follicular size of at least 30mm, as determined by ultrasound and rectal palpation, were allocated to one of three treatment groups. They were 35 2.2mg Deslorelin implant, hCG (5000 iu) and untreated

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controls. It can be seen that ovulation commonly occurred around 2 days for the Deslorelin implanted and hCG injected mares. Untreated controls took significantly longer to ovulate from both implantation and from the start of 5 oestrus than the treated groups. It appears that the untreated controls were in oestrus longer than treated animals.

TABLE 1

STUDY 1: Mean values of oestrus characteristics for three ovulation induction treatments.

10

<u>Characteristics</u>	<u>TREATMENTS</u>		
	LHRH	hCG	Control
No. day oestrus	5.88 ± 1.27	5.46 ± 0.96	6.90 ± 2.42
Day OV	4.13 ± 0.35 ^a	4.40 ± 0.96 ^a	6.10 ± 1.79 ^b
15. 30mm to OV	2.13 ± 0.35 ^a	2.00 ± 0.00 ^a	3.70 ± 1.49 ^b
No. Ov's	0.90 ± 0.56	1.10 ± 0.32	1.10 ± 0.32

Example 5

Mares with follicular size of at least 30mm, as determined by ultrasound and rectal palpation, at two locations (CSU and 20 UCD) were allocated to one of five treatment groups. These treatment groups were a placebo implant, and implants containing 1.2mg, 1.7mg, 2.2mg and 2.7mg of Deslorelin. In this example the implant comprised finely ground calcium phosphate dihydrate, 8% by weight Lubritab and, where appropriate, the Deslorelin. A 25 summary of the results obtained is provided in Table 2 which shows the mean time in hours to ovulation, standard deviation in hours of the time to ovulation, the number of mares in the sample and the percentage of mares ovulating within 48 hours.

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Table 2

Summary statistics* for the time to ovulation by study location and Deslorelin dose treatment group.

Centre	Treatment Group No. (Deslorelin dose, mg)				
	1 (0)	2 (1.2)	3 (1.7)	4 (2.2)	5 (2.7)
CSU	-				
x	68.00	49.00	48.00	46.91	44.00
s	38.74	8.02	11.44	3.62	9.34
n	12	12	12	11	12
P	50.0	75.0	83.3	100.0	100.0
UCD	-				
x	91.50	66.00	58.50	46.50	58.29
s	35.68	37.40	45.10	10.01	32.81
n	8	8	8	8	7
P	25.0	75.0	87.50	87.50	85.71
Combined	-				
x	77.40	55.80	52.20	46.74	49.26
s	38.44	25.01	29.21	6.81	21.50
n	20	20	20	19	19
P	40.0	75.0	85.0	94.7	94.74

*Summary statistics include the mean (x) and standard deviation (s) of the time to ovulation, the sample size (n), and the percent of mares ovulating within 48 hours (P).

The mares were mated and Table 3 summarises the pregnancy among the mares. This table provides the sample size, the number and percent of mares pregnant through a first cycle and the number and percent of mares pregnant through a second cycle.

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Table 3

Summary* of pregnancy among study mares by study location and Deslorelin dose treatment group.

	Center	Treatment Group No. (Deslorelin dose, mg)					
		1 (0)	2 (1.2)	3 (1.7)	4 (2.2)	5 (2.7)	
10	CSU	n	12	12	12	11	12
		m_1	5	8	8	8	8
		P_1	41.7	66.7	66.7	72.7	66.7
		m_2	7	11	11	10	9
		P_2	58.3	91.7	91.7	90.9	75.0
15	UCD	n	8	8	8	8	7
		m_1	6	5	4	5	4
		P_1	75.0	62.5	50.0	62.5	57.1
		m_2	7	7	**6	**7	**5
20		P_2	87.5	87.5	75.0	87.5	71.4
	Combined	n	20	20	20	19	19
		m_1	11	13	12	13	12
25		P_1	55.0	65.0	60.0	68.4	63.2
		m_2	14	18	**17	**17	**14
		P_2	70.0	90.0	85.0	89.5	73.7

30 * Summary includes the sample size (n), the number (m_1) and percent (P_1) of mares pregnant through the first cycle, and the number (m_2) and percent (P_2) of mares pregnant through the second cycle.

** One mare in each of these study groups was not bred

35 back.

- 10 -

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the 5 invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

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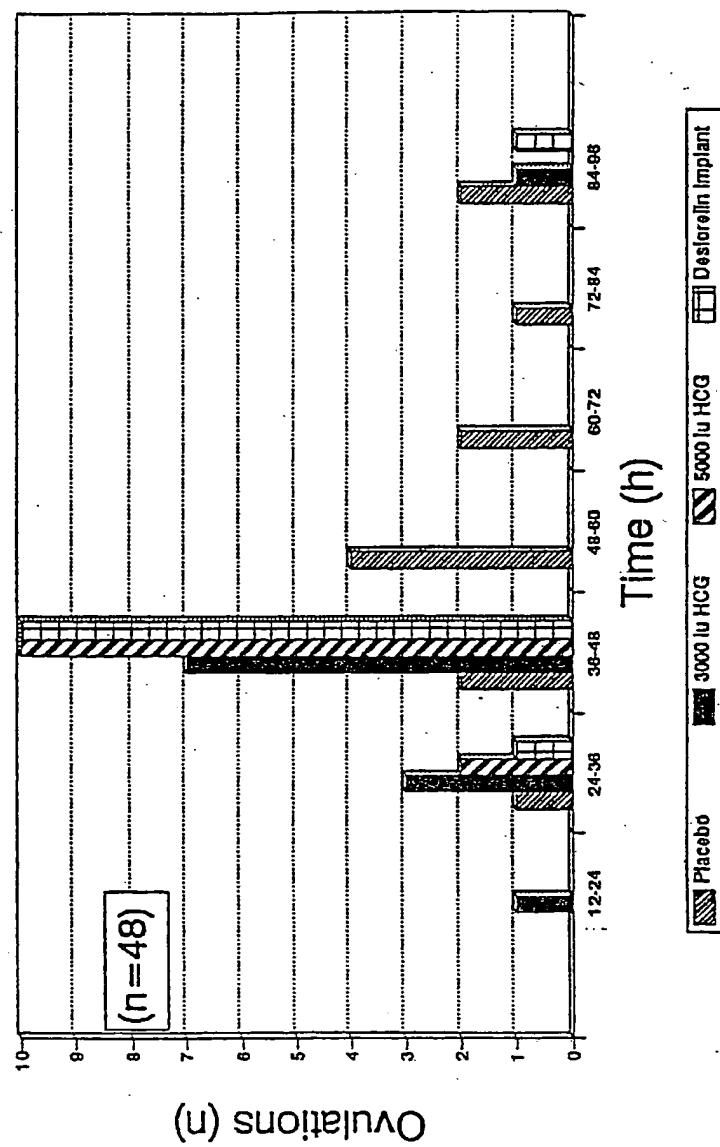
CLAIMS:

1. A method for the controlled induction of ovulation in mares comprising implanting into a mare having a maturing ovarian follicle a solid biocompatible implant comprising a solid carrier and an effective amount of LHRH or an agonist of LHRH.
2. A method as claimed in claim 1 in which the LHRH agonist is Deslorelin.
3. A method as claimed in claim 1 in which the LHRH agonist is present in the implant in an amount of from 1.0 to 5.0 mg.
4. A method as claimed in claim 3 in which the LHRH agonist is present in the implant in an amount of 1.5 to 3.0 mg.
5. A method as claimed in claim 4 in which the LHRH agonist is present in the implant in an amount of 2.0 to 2.4 mg.
6. A method as claimed in claim 1 in which the solid carrier comprises a biologically absorbable inorganic salt and an organic tablet release compound.
7. A method as claimed in claim 1 in which the implant is embedded subcutaneously into the mare.
8. A method as claimed in claim 7 in which the implant is embedded into the mare through a tubular needle inserted into the mare, the implant being pushed down the needle with an obturator as the needle is withdrawn.
9. A solid biocompatible implant for controlling the induction of ovulation in mares, the implant comprises a biologically absorbable solid and LHRH or an agonist of LHRH.
10. A biocompatible implant as claimed in claim 1 in which the LHRH agonist is Deslorelin.
11. A biocompatible implant as claimed in claim 9 in which the LHRH agonist is present in the implant in an amount of from 1.0 to 5.0 mg.

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12. A biocompatible implant as claimed in claim 11 in which the LHRH agonist is present in the implant in an amount of from 1.5 to 3.0 mg.
13. A biocompatible implant as claimed in claim 11 in
5 which the LHRH agonist is present in the implant in an amount of from 2.0 to 2.4 mg.
14. A biocompatible implant as claimed in claim 9 in
which the solid carrier comprises a biologically
absorbable inorganic salt and an organic tablet release
10 compound.
15. A biocompatible implant as claimed in claim 14 in
which the inorganic salt is selected from the group
comprising calcium phosphate dihydrate, calcium phosphate,
sodium sulphate and calcium carbonate.
16. A biocompatible implant as claimed in claim 14 in
15 which the organic tablet release compound is selected from
the group comprising a fatty acid and a hydrogenated
vegetable oil.
17. A biocompatible implant as claimed in claim 9 in
20 which the implant is substantially cylindrical having a
diameter of from 0.5 to 5.0 mm and a length of from 1.0 to
6.0 mm.

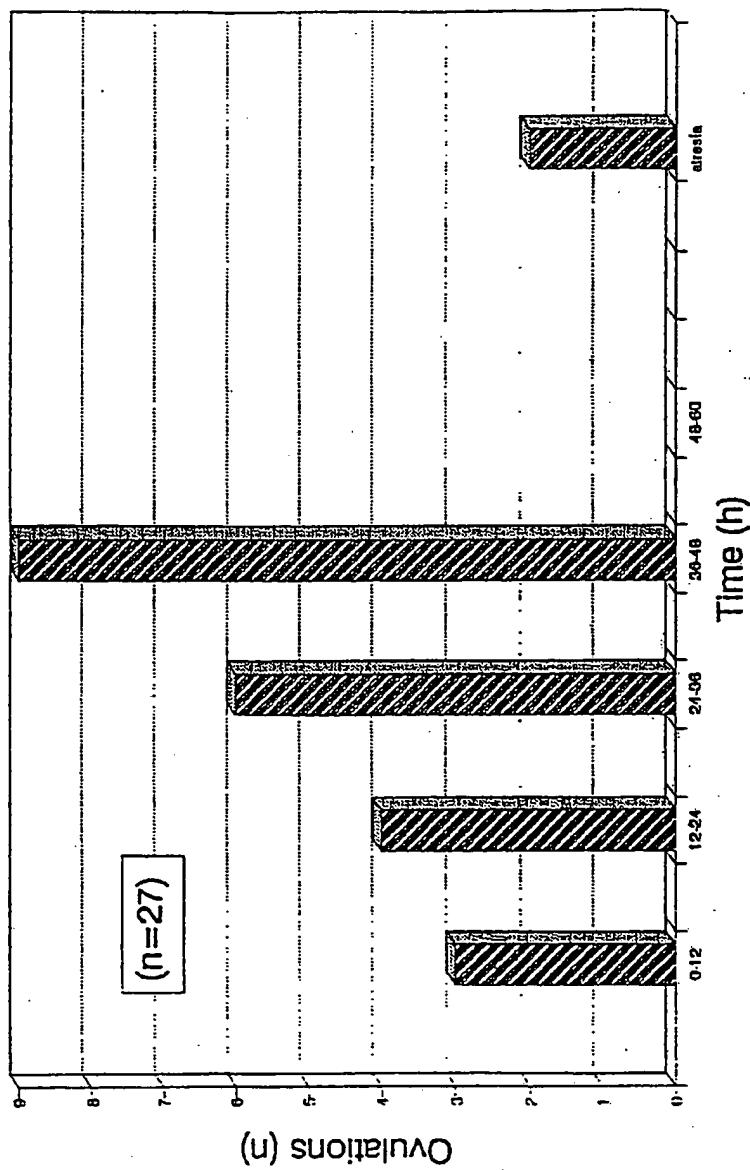
Fig 1: Time to ovulation
Treatment: Follicle diameter 40mm



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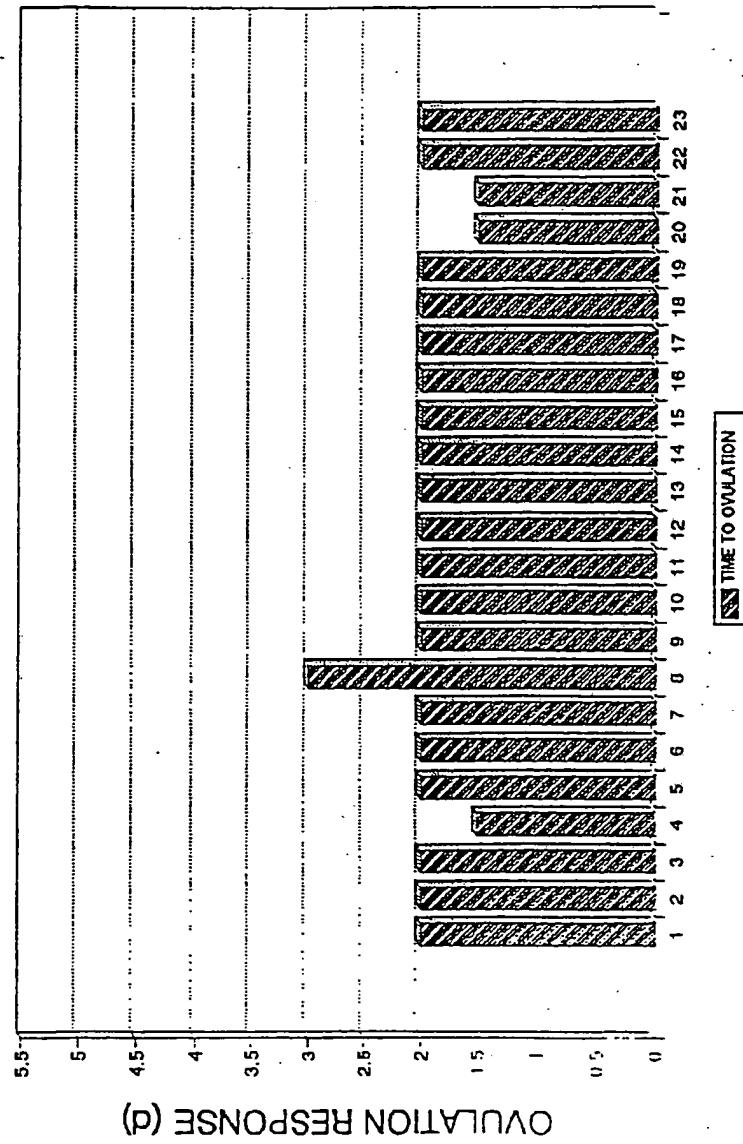
Fig 2: Time to ovulation after treatment
GnRH Implant 2.25 mg



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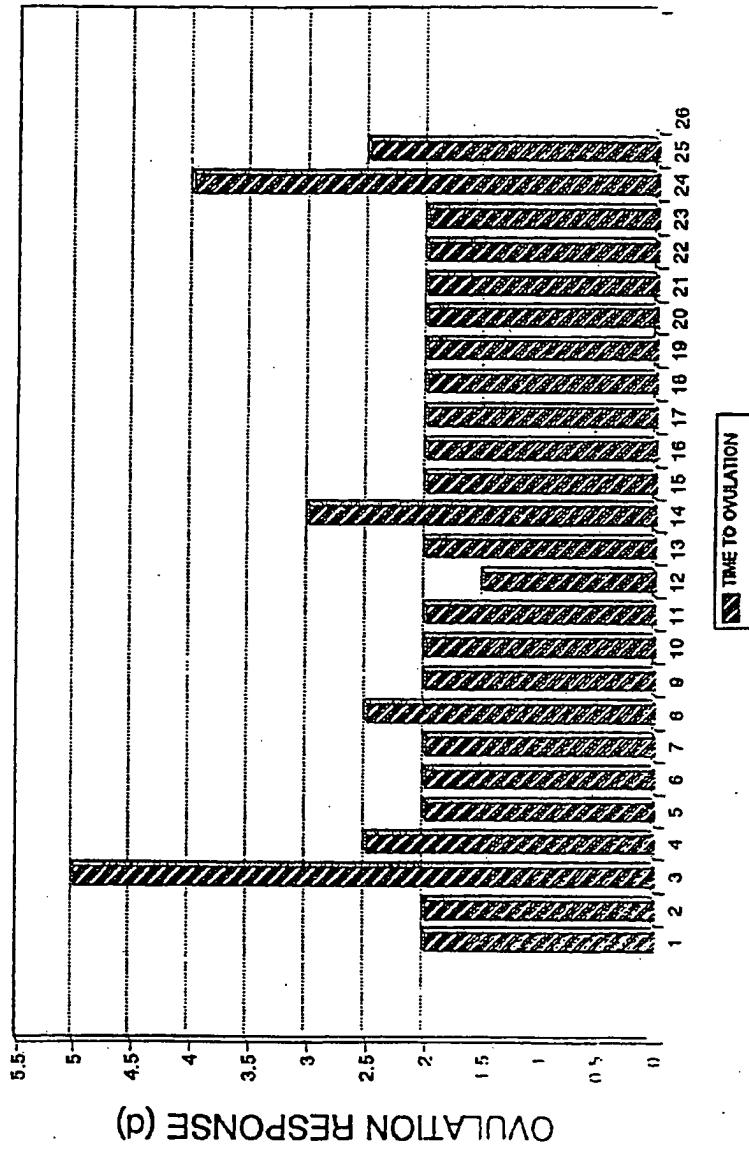
OVULATION RESPONSE TO TREATMENTS
2.2 MG(#100)
FIG 3



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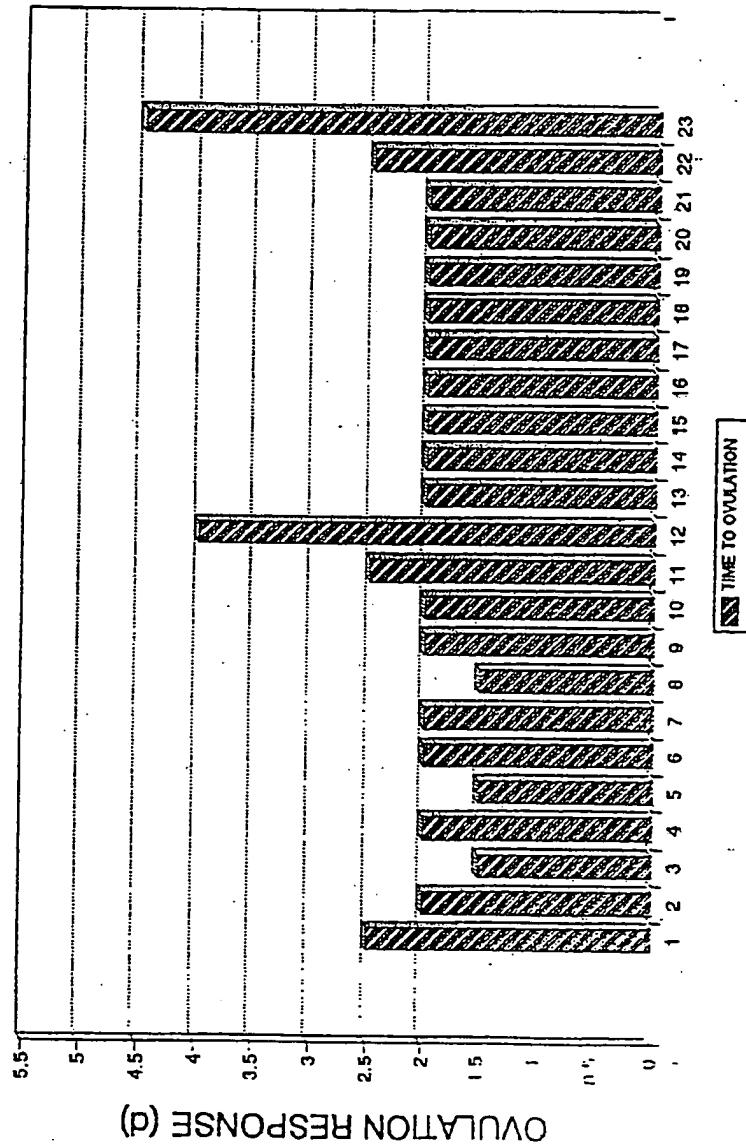
OVULATION RESPONSE TO TREATMENTS
1.3MG(#102)
FIG 4



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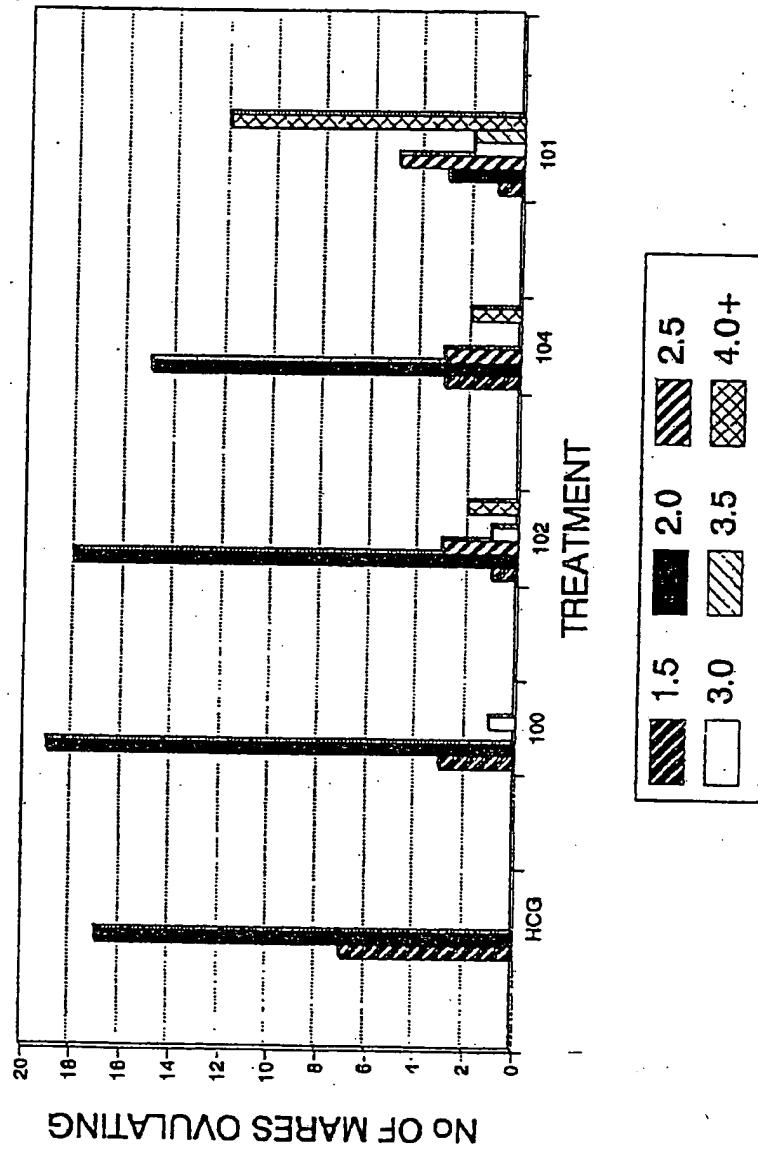
OVULATION RESPONSE TO TREATMENTS
1.6MG (#104)
FIG 5.



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OVULATION RESPONSE
Time to ovulation (d)



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU92/00557

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl. ⁵ A61D 19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61D 19/00, 7/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT
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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Derwent Abstracts Accession No. 87-329107/47, Class P32, EP,A,246910 (GENE LINK AUST. LTD.) 25 November 1987 (25.11.87). Page 6 lines 2-11	1,9
X	AU-B-57327/86 (586252), (THE UNIVERSITY OF MELBOURNE) 13 November 1986 (13.11.86). Page 3 lines 25-27	1,7-9
A	US 4589402, (SERONO LABORATORIES, INC.) 20 May 1986 (20.5.86)	1-17
A	GB,A,2166951, (GLAXO GROUP LIMITED) 21 May 1986 (21.5.86)	1-17

Further documents are listed
in the continuation of Box C.

See patent family annex.

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Date of the actual completion of the international search
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Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
A	Derwent Soviet Inventions Illustrated, Section 1, Chemical, Vol. X, No. 14, Issued 12 May 1976, Pharmaceuticals, p. 1, SU 475136 (LIVESTOCK FARM RES) 19 September 1975 (19.9.75)	1-17
A	Derwent Soviet Inventions Illustrated, Section 1, Chemical, Vol. U, No. 37, Issued 18 October 1973, Pharmaceuticals, p. 4, SU 367866 (LIVESTOCK BREEDING RES. INST.) 30 March 1973 (30.3.73)	1-17

INTERNATIONAL SEARCH REPORT
Information on patent family memb.

International application No.
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
AU 57327/86	GB 2174600 US 4997816
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